REMARKS

In the instant Office Action, claims 1-16 and 19 are listed as pending, claims 2, 5-8 and 12-14 are listed as withdrawn from consideration, and claims 1, 3, 4, 9-11, 15, 16, and 19 are listed as rejected. In response to the instant Office Action, Applicant has amended claims 1, 4, 11, and 15.

Applicant expressly reserves the right to reclaim any subject matter cancelled or removed from consideration by the foregoing amendments by reintroducing said subject matter in the present application and/or by filing a subsequent application.

Applicant states that the above amendments neither introduce new matter nor require any change of inventorship pursuant to 37 C.F.R. §1.48(b).

Initially, Applicant appreciatively notes the following actions of the Examiner in the instant Office Action:

- The Examiner withdrew the "ODP" rejection of claim 1 over USP 6,903,186.
- The Examiner withdrew the provisional "ODP" rejection of claim 1 over S.N. 11/145,782.
- The Examiner withdrew the rejection of claim 1 under 35 U.S.C. §103 over USP 6,214,547 to Kjeldsen, at least for purposes of the instant Office Action.

I. Rejection of Claims 1, 3, 4, 9-11, 15, 16, and 19 under 35 U.S.C. §112, first paragraph

In the instant Office Action, the Examiner has rejected claims 1, 3, 4, 9-11, 15, 16, and 19 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant respectfully traverses this rejection.

In particular, claims 1, 3, 4, 9-11, 15, 16, and 19 were rejected on the basis that Applicant failed to provide relevant data compiled using the assay described in the specification evidencing the claimed compounds' ability to perform as asserted. Without conceding the correctness of the

stated rejection, Applicant submits herewith the affidavit of Dr. John E. Taylor, pursuant to Rule 132, introducing experimental data illustrating the claimed compounds' ability to perform as asserted. As such, there is sufficient basis for concluding that the claimed compounds of the instant Application are capable of binding to the GLP-1 receptor. On this basis alone, Applicant respectfully submits that the Examiner's concerns regarding the utility of the claimed invention are adequately addressed.

With respect to the claimed compounds for which Applicant has not submitted experimental data, it is apparent that it would not require "undue experimentation" for a skilled artisan to follow the same procedure as outlined in the instant Application to obtain similar experimental data. Indeed, in the instant Office Action, the Examiner has acknowledged this point, as follows:

> [T]he examiner would agree that to synthesize one peptide and to test that one peptide (according to the disclosed assay) would not require "undue experimentation." Further, to synthesize ten peptides, and to test each of them would probably also not require undue experimentation.

For instance, with respect to claim 9, Applicant has submitted experimental data for six of the eleven claimed compounds. With respect to the five claimed compounds of claim 9 for which no experimental data has been submitted, in line with the Examiner's above statement, it would not require "undue experimentation" for a skilled artisan to synthesize those compounds and to test that each of those compounds (according to the disclosed assay) for the asserted activity. In the absence of any indication in the instant Office Action that the disclosed assay would entail undue experimentation, other than the alleged unpredictability in the art, Applicant submits that all of the claimed compounds of claim 9 are sufficiently enabled – *i.e.*, there is no objective indication that the skilled artisan would be unable to follow the disclosed assay without undue experimentation.

What is puzzling to Applicant is the Examiner's next statement that "[b]ut to synthesize, e.g., 1 million peptides, and to test each of them would require undue experimentation" (emphasis original). So, the Examiner's reasoning is that it would probably not require "undue experimentation" to test ten peptides, but that it would require "undue experimentation" to test 1 million peptides. However, even with respect to a great many compounds, the skilled artisan

would view the performance of the disclosed assay to comprise no more than a routine part of normal pharmaceutical research. To the extent the Examiner is judging "undue experimentation" on the basis of the number of compounds to be tested, it is respectfully submitted that the Examiner is applying arbitrary and overly stringent standard of enablement.

Even more troubling is the Examiner's next statement that "even if a chemist (or group of chemists) were to undertake such a massive effort, the fact is that even then the skilled artisan would not be able to reliably 'predict' that even one of those million peptides would bind to the GLP-1 receptor." (emphasis original). That is, according to the Examiner, even if a group of chemists were to follow the disclosed assay to synthesize and test a certain number of compounds as a routine part of normal pharmaceutical research, "even then the skilled artisan would not be able to reliably 'predict' that even one of those million peptides would bind to the GLP-1 receptor." But if the skilled artisan is able to synthesize and test any one of the claimed compounds (according to the disclosed assay) for which Applicant has not submitted experimental data, and if the skilled artisan is able to do so without "undue experimentation," then the skilled artisan is enabled to make and use the compound, without having to "predict" whether that compound would bind to the GLP-1 receptor. In other words, Applicant does not understand the Examiner's reasoning that the skilled artisan would be left to "predict" whether the claimed compounds would bind to the GLP-1 receptor when that skilled artisan can simply follow the disclosed assay to determine such activity.

The Examiner then states that "The reality in pharmacology is that minor changes in structure often eliminate activity. One cannot 'predict' pharmacological efficacy merely by viewing the structure of a compound; the reality of this is not changed merely by the suggestion of an assay method." Again, the Examiner is assuming that the skilled artisan would opt to "predict" the claimed compounds' asserted activity based on structure/activity relationships, even when Applicant has provided enabling disclosure to synthesize and test all of the claimed compounds. By providing sufficiently clear and easy to follow (*i.e.*, enabling) disclosure to synthesize and test all of the claimed compounds in the instant Application, Applicant is not asking the skilled artisan to "predict" pharmacological efficacy merely by viewing the structure of a compound; the skilled artisan is presumed to follow the disclosed assay.

In sum, instead of ***showing*** that it would require undue experimentation to follow the disclosed assay to make and test the claimed compounds, the Examiner has simply ***presumed*** that it would require undue experimentation on the basis that the art is unpredictable. However, as explained in M.P.E.P. §2164.03, the "predictability or lack thereof" in the art simply refers to "the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention"; and "[t]he scope of the required enablement varies with the degree of predictability involved." And it is a mere tautology to state that the skilled artisan would be unable to "predict" the claimed compounds' asserted activity because the art is unpredictable. The real question is, even assuming the art is unpredictable, whether Applicant has provided enough disclosure to enable the skilled artisan to make and use the claimed invention. In the instant Office Action, the Examiner has acknowledge that "undue experimentation" would not be required to *synthesize* any one of the claimed peptides. *See* page 4, lines 2-3, of the instant Office Action. With respect to the "how to use" prong of the enablement requirement, as discussed hereinabove, the Examiner has failed to *show* that the disclosed assay to test the claimed compounds' asserted activity is somehow flawed, or would otherwise entail "undue experimentation." Therefore, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of nonenablement. On this alternative ground, Applicant respectfully requests reconsideration and withdrawal of this rejection.

If the Examiner is inclined to maintain the rejection of claim 1, or any other pending claims, under 35 U.S.C. §112, first paragraph, in the next office action, Applicant respectfully requests that the Examiner show why the skilled artisan must engage in "undue experimentation" to synthesize and test any one of the claimed compounds according to the disclosed assay, other than the number of compounds (*i.e.*, according to the Examiner, to synthesize and test ten compounds would probably not require undue experimentation; however, to synthesize, e.g., 1 million peptides, and test each of them would require undue experimentation).

II. Rejection of Claim 11 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claim 11 as being indefinite. In particular, the Examiner has alleged that the phrase "effective amount" renders claim 11 indefinite as to the objective(s) of the

amount. Without conceding the correctness of the Examiner's allegation, in the instant Amendments Applicant has amended claim 11 to delete the phrase "effective amount." Support for the amendment can be found in the specification at page 9, lines 25-25. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

III. Rejection of Claims 1-2 and 11 under 35 U.S.C. §102(b) over USP 5,545,618

The Examiner has maintained the rejection of claims 1-2 and 11 under 35 U.S.C. §102(b) over U.S. Pat. No. 5,545,618 to Buckley ("Buckley"). In maintaining the rejection, however, it does not appear that the Examiner considered Applicant's argument (of the response filed 5/18/06) with respect to the paragraph (iii) of the proviso to claim 1, which argument is copied hereinbelow:

> Further, Applicant respectfully directs the Examiner's attention to paragraph (iii) of the proviso to claim 1, which requires that "at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH_2 or hGLP-1(7-36, -37 or -38)OH". Thus to the extent that the Examiner alleges that, despite the foregoing peptide length limitation, claim 1 remains anticipated by Buckley, paragraph (iii) affirmatively precludes the conclusion that the scope of the claims may correctly be interpreted to read on GLP-1(7-34) or GLP-1(7-35) [or GLP-1(7-37)].

To dispel the Examiner's doubts as to whether claim 1 clearly excludes native GLP-1(7-34), GLP-1(7-35) and GLP-1(7-37), in the instant Amendments, Applicant has amended paragraph (iii) of the proviso to claim 1 as follows:

> (iii) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, <u>-34, -35,</u> -37 or -38)NH_2 or hGLP-1(7-36, <u>-34, -35,</u> -37 or -38)OH

As amended, claims 1-2 and 11 are not drawn to native GLP-1 sequences *of any length*. In view of this amendment, the rejection of claims 1-2 and 11 are obviated. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

IV. Rejection of Claims 1-2 and 11 under 35 U.S.C. §103 over Buckley

The Examiner has maintained the rejection of claims 1-2 and 11 under 35 U.S.C. §103 over Buckley. Without conceding the correctness of this rejection, Applicant has amended claims 1, 4 and 15 to better distinguish the instant Application from the cited reference. In particular, claim 1 has been amended to delete "Ala" from the definition of A^8 and to delete "Gly" from the definition of A^{35}. Likewise, claim 4, which ultimately depends on claim 1, has been amended to delete "Ala" from the definition of A^8. Likewise, claim 15, which depends on claim 1, has been amended to delete the following two compounds: $(Aib^{35})hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:71); $(\beta\text{-}Ala^{35})hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:72). With these amendments, claim 1, and all claims dependent thereon, are restricted to GLP-1 analogues bearing modifications at both positions 8 and 35.

In this respect, Applicant has attached an article published in the name of the inventor of the instant Application, entitled "Glucagon-Like Peptide-1 Analogs with Significantly Improved *in vivo* Activity," published in *Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium*, June 9-14, 2001, San Diego, California, U.S.A., wherein, at pages 670-71, it is stated:

> [A]nalogs bearing modifications at both positions 8 and 35 … have much longer plasma half-life than mono-substituted compounds … retain receptor potency of the native hGLP-1 … [and] enhanced the insulin response to elevated glucose [levels].

As stated at page 2, lines 15-19 of the instant Application, an objective of the inventor of the instant Application was to provide a more metabolically stable GLP-1 analogs since "[human] GLP-1 is … metabolically unstable, having a plasma half-life ($t_{½}$) of only 1-2 min *in vivo*." Buckley does not teach or suggest this improvement. Nor is there any motivation in Buckley to look to other references to arrive at the claimed compounds in the instant Application. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

V. Rejection of Claims 1 and 11 under 35 U.S.C. §103 over WO 98/08871

The Examiner has maintained the rejection of claims 1 and 11 under 35 U.S.C. §103 over WO 98/08871 to Knudsen ("Knudsen"). In view of the instant Amendments wherein Applicant has amended claims 1, 4 and 15, thereby restricting GLP-1 analogues of the instant Application to bear modifications at both positions 8 and 35, it is respectfully submitted that this rejection has been obviated. For instance, none of the GLP-1 analogs disclosed in Knudsen – *i.e.*, those listed on pages 19-30 of Knudsen – bears modifications at both positions 8 and 35. That is, none of the compounds disclosed in Knudsen falls within the scope of claim 1, as amended. Nor is there any motivation in Knudsen to look to other references to arrive at the claimed compounds in the instant Application. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

VI. Remarks regarding reference previously submitted to the Patent Office

In the final page of the instant Office Action the Examiner states that reference "EB" (Argentinian Patent No. AR256113M) from the previously-submitted IDS was stricken from the IDS because the reference was either not submitted or was submitted without translation. Applicant notes that in the Sixth Supplementary IDS submitted on July 12, 2006, Applicant explained that reference "EB" claims the benefit of U.S. Patent Application Serial No. 08/407,831, and according to information available via the U.S. Patent Office PAIR site, U.S. Patent Application Serial No. 08/407,831 issues as U.S. Patent No. 5,705,483 and is reasonably believed to be an English language equivalent for reference "EB."

CONCLUSION

All issues raised in the instant Office Action are believed to have been addressed. Reconsideration of the instant Office Action, entry of the amendments submitted herewith, and allowance of all pending claims are respectfully requested. Prompt and favorable action is solicited.

Should Examiner Lukton deem that any further action be desirable with respect to these matters, he is requested to telephone the Applicant's undersigned representative.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-0590.

Respectfully submitted,

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